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PROPOFOL AND FENTANYL COMPARED TO MIDAZOLAM AND FENTANYL DURING THIRD MOLAR SURGERY

by

Larry Paul Parworth

A Thesis submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Science in the Department of Oral and Maxillofacial Surgery.

Chapel Hill

1996

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LARRY PAUL PARWORTH. Propofol And Fentanyl Compared To Midazolam And Fentanyl During Third Molar Surgery. (Under the direction of David E. Frost)

ABSTRACT

Fifty-seven patients undergoing removal of third molars with intravenous sedation between November 1994 and December 1995 randomly received either propofol and fentanyl (P + F) or midazolam and fentanyl (M + F). Twenty-four received P + F and thirty-three received M + F. Pre-operatively, patient demographics, Corah anxiety scores and physiologic parameters were obtained. All patients were titrated to the same endpoint for sedation. Intra-operative physiologic parameters, cooperation, alertness and pain scores were assessed. Post-operative recovery and degree of amnesia were determined. There were no statistically significant differences in patient demograhpics and surgical characteristics between groups. The P + F group was statistically significantly less cooperative than the M + F group. Pain during injection of propofol was a significant adverse side effect. Both groups experienced a small percentage of apneic episodes but mechanical ventilation was never required. There was no difference in recovery between groups as assessed by Treiger dot test and psychomotor recovery scores. The degree of retrograde amnesia was higher for the M + F group although the differences were not statistically significant. Sedation was rated good to excellent by the patient, surgeon and observer and there were no statistically significant differences between groups. Propofol appears to be a safe and efficacious drug for use in outpatient oral surgical procedures.

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INTRODUCTION

The ability to competently and proficiently administer anesthesia is a vital part of an oral and maxillofacial surgeon's practice. Oral and Maxillofacial Surgery is unique in that for outpatient surgical procedures the clinician functions in the dual role of anesthestetist and surgeon.

Intravenous sedation or general anesthesia is indicated for relief of anxiety associated with outpatient surgical procedures. Conscious sedation is a method of depression of the central nervous system which allows the operator to carry out a surgical procedure during which the patient retains protective reflexes.[1] Conscious sedation with local anesthesia is a safe alternative to general anesthesia for the control of peri-operative pain and anxiety in outpatient surgery.[2,3] The ideal anesthetic technique for ambulatory surgery should provide rapid onset and stable operating conditions while ensuring rapid recovery of protective reflexes and cognitive and psychomotor functions.[16] A survey of 500 fellows of the American Dental Society of Anesthesiology (ADSA) by Dionne in 1988 revealed 82 distinct drugs and combinations reported for intravenous sedation and anesthesia.[4] As new anesthetic agents have been introduced, different techniques have been developed for use in ambulatory surgery.

Propofol is a short acting intravenous anesthetic with a rapid onset of action, short elimination half-life, and inactive metabolites.[7] Propofol (2,6 di-isopropyl phenol) was made available in the United States in 1989 under the proprietary name Diprivan (Stuart, Wilmington, DE).[5] The 1% solution of propofol is in an aqueous solution of 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide.[6] Propofol is recommended to be administered via a continuous infusion technique. A review of the

literature reveals little data which examines the safety and efficacy of conscious sedation with propofol during outpatient oral surgical procedures.

Rodrigo and Johnson investigated the suitability of propofol for conscious sedation in 31 patients undergoing bilateral third molar surgery.[7] Patients were randomly given either propofol or midazolam for sedation at the first visit, and the alternative at the second visit. The drugs were administered until partial ptosis of the eyelids (Verril's sign) occured. The investigators concluded the advantages of propofol over midazolam were the ease of altering the degree of sedation and the quick recovery. The mean recovery time was 22 minutes following sedation with propofol and 49 minutes following midazolam, which was statistically significant ($p < 0.001$). Disadvantages of propofol were pain at the injection site (58% incidence), increased talkativeness and extra equipment and cost. The number of patients who had complete amnesia was higher in the midazolam group, but the difference was not statistically significant. The study did not have specific inclusion and exclusion criteria. Narcotics were not used as adjuncts to sedation.

Valtonen *et al* compared the infusion of propofol with intravenous (I.V.) boluses of diazepam in 12 patients undergoing elective removal of bilateral lower third molars.[48] Patients were randomly assigned to receive either propofol or diazepam sedation on the first occasion and received the alternate sedative agent on their second visit. The anesthesia was supplemented with local anesthesia. Plasma catecholamine, vasopressin and cortisol levels were measured from repeated blood samples before sedation, 15 minutes after the start of the I.V., at the enpoint of sedation, 15 minutes after the start of the surgery and 180 minutes after the sedation. No cardiovascular or airway problems occured. Six patients had pain at the injection site during propofol infusion compared to 0 with diazepam ($p = 0.0069$). Recovery from propofol sedation was more rapid than diazepam (visual analog scale 6 cm vs 4 cm at 60 min post-op, $p < 0.01$). Propofol provided improved amnesia compared to the diazepam at the time of tooth extraction (9

versus 3, $p = 0.02$). Eight of the twelve patients preferred sedation with propofol. Plasma adrenaline, noradrenaline and cortisol levels were equally depressed after both sedative agents. Patients entered into the study were ASA I and were excluded if they reported a history of drug allergy, pregnancy, concurrent illness and acute or chronic drug therapy. Patient cooperation or depth of sedation during the procedure were not studied.

Meyers *et al* compared propofol and methohexital anesthesia for deep sedation during outpatient third molar surgery.[34] All subjects received fentanyl and midazolam titrated to effect. Patients were then randomly assigned to receive either methohexital or propofol until partial eyelid ptosis, slurred speech and relaxed posture were achieved. Physiologic data between groups showed no stastically significant differences except for a dramatic increase in heart rate in the methohexital group. Quicker recovery was demonstrated by the patients who received propofol (Treiger dot test at 20 min post-op, 1 dot vs 6 dots missed, $p < 0.05$). Patient cooperation and degree of CNS depression during the procedure were not studied. Amnesia to clinical procedures was not evaluated. All patients entered into the study were over the age of 18 and were ASA I or II. There were no exclusion criteria mentioned.

To establish the efficacy of propofol for use as an outpatient agent, data must be available from well designed clinical studies. Midazolam and fentanyl are used by many oral and maxillofacial surgeons for sedation during the removal of third molars. For this reason this combination was selected as the comparative drug regimen. This study compared midazolam to propofol, each in combination with fentanyl, as sedative agents during elective third molar surgery

REVIEW OF THE LITERATURE

Historical Perspectives

One of the earliest accounts of intravenous anesthesia was in 1657 when Christopher Wren injected opium intravenously by means of a quill and bladder in dogs and humans, rendering them unconscious.[8] Pierre-Cyprien Ore administered chloral hydrate intravenously for a surgical procedure in 1874. Olson described a method for administration of thiopental for anesthesia during oral surgical procedures in 1943.[8] Jorgenson in 1945 described a technique where pentobarbital was titrated and a fixed dose of meperidine and scopalamine was administered.[13] The developement of methohexital in 1957 , an ultrashort- acting barbituate, with a rapid onset of anesthesia and a short recovery, led to methohexital becoming the drug of choice for office anesthesia over thiopental.[11] In 1966 Shane developed a popular technique which involved a combination of alphaprodine, hydroxyzine, and atropine administered intravenously and followed by increments of 10 to 20 mg of methohexital.[12] In 1968 , Foreman *et al* developed a technique by first obtaining a baseline level of sedation with diazepam, followed by incremental titration of methohexital to achieve the desired level of sedation.[9]

A major advancement in the pharmacology of anesthesia was the synthesis of midazolam in 1976 by Freyer and Walser. Midazolam was the first water-soluble benzodiazepine used clinically in the 1980's.[23] Midazolam eliminated many of the undesirable characteristics of diazepam.[10] The major side effects of diazepam include venous irritation and thrombophlebitis. The amnestic effects of midazolam are much more

predictable and the prolonged hangover seen with valium is less evident with midazolam because of its inactive metabolites.

Propofol is the most recent intravenous anesthetic to be introduced. Work in the early 1970s on substituted derivatives of phenol with hypnotic properties resulted in the developement of 2,6 di-isopropofol.[16] The first clinical trial with propofol was reported by Kay and Rolly in 1977.[16] Their initial paper described 4 separate sequential investigations in man. The first trial involved determined that the mean effective induction dose was 0.94 mg/kg of I.C.I.35868 (2,6 di-isopropofol) given over a mean time of 47 seconds. Pain was the only side effect recorded. In the second trial, 26 adults were given .75 mg/kg of I.C.I.35868 in 30 seconds which induced sleep in a mean time of 3 minutes 11 seconds with a significant reduction in ventilation. Over 50% of the patients complained of pain at the site of injection. A third trial investigated the effect of respiratory drive compared to that of methohexital in 2 anesthetised patients; 0.25 mg/kg of I.C.I. 35868 produced less respiratory drive than 0.33 mg/kg of methohexital. The final trial involved an incremental dose study that evaluated the effects of repeated doses of I.C.I. 35868 in 15 patients undergoing operation under local anesthesia. There was little evidence of accumulation and very little side effects. Propofol became available in the U.S. in 1989 and has gained popularity for use in oral surgical procedures.[17]

Metabolism

Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate.[24] Less than 1 percent is excreted unchanged in the urine and only 2 percent is excreted in the feces. Veroli *et al* conclusively demonstrated that extrahepatic routes of metabolism do exist.[46] Propofol was administered to patients during the anhepatic phase of orthoptic liver transplantation and discovered propofol metabolites in the urine while the liver was excluded from the circulation. The extrahepatic site of metabolism is yet to be determined. The two principal biotransformation pathways of midazolam metabolism involve either hepatic microsomal oxidation or glucuronide conjugation. Certain population characteristics such as old age, the co-administration of other drugs like cimetidine and hepatic cirrhosis inhibit the enyme responsible for oxidation of midazolam.[8] Habitual alcohol consumption increases the clearance of midazolam since higher doses of midazolam are required for maintainance of anesthesia in patients with chronic alcohol use.[25] The metabolites are excreted in the urine in the form of glucoronide conjugates. Only very small amounts of midazolam are excreted unchanged in the urine. Metabolites of both midazolam and propofol have little activity.[8,26]

Pharmacokinetics

Pharmacokinetics is the quantitative study of absorption, distribution, metabolism and excretion of drugs and their metabolites. Pharmacokinetics of intravenous drugs are influenced by the volume of distribution (Vd) for that drug and the clearance of that drug from the body. The sum of the compartment volumes is the apparent volumes of

distribution and is a proportionality constant relating the drug concentration in blood or plasma to the total amount of drug in the body.[16] One compartment model consists of two spaces, named the central compartment and the peripheral compartment. The central compartment includes the intravascular fluid and highly perfused organs such as the brain, heart, liver and kidneys. In the adult these tissues account for 10% of body mass and recieve 75% of the cardiac output. The peripheral compartment includes the peripheral body tissues. In the three compartment model, the peripheral compartment is further divided into muscle and fat. Compartment volumes are defined in terms of apparent volumes and do not refer to absolute anatomic volumes. Binding to plasma protiens, a high degree of ionization and poor lipid solubility limit passage of drug to tissues (peripheral compartment), thus maintaining high plasma concentrations (central compartment) and a small calculated volume of distribution.[18] Non-ionized lipid soluble drugs such as thiopental and diazepam transfer from the circulation to the tissues such that plasma concentrations are low and the calculated Vd is large.

Propofol has a unique pharmacokinetic profile that contributes to its favorable clinical characteristics. Of great importance is the rapid metabolic clearance of propofol, which is approximately ten times faster than thiopental.[19] The metabolic clearance of propofol exceeds hepatic blood flow, indicating that propofol has extra-hepatic sites of metabolism and elimination.[18] The clearance of propofol is extremely high at 21.4-30 ml/kg/min compared to the clearance of midazolam at 6-8ml/kg/min.[19,20] Plasma levels of propofol decline rapidly after an initial bolus due to the redistribution from highly perfused tissues into the less perfused sites (e.g.muscle).[16] This principal is demonstrated by propofol's high distribution clearance of 3-4 L/kg/min.[18] Factors known to influence the pharmacokinetics of both propofol and midazolam include age, gender and weight.[8,27] The clinical duration of propofol does not appear to be greatly affected by hepatic or renal dysfunction.[17] Morcos and Payne investigated induction of anesthesia with propofol compared in normal and renal failure patients.[28] The pharmacokinetics of propofol was

similar in both groups. Cockshott *et al* investigated propofol infusions in patients with cirrhosis and concluded that pharmacokinetics of propofol was not markedly affected compared to healthy patients.[29] Pharmacokinetics of midazolam are influenced by hepatic disesase.[8] Midazolam's Vd , clearance or elimination half life are not significantly different between normal and renal failure patients.[22] The elimination half-life of propofol is long (6.3 hrs) compared to midazolam's elimination half-life of 1-4 hours, yet recovery from prolonged administration of propofol is reported as being more rapid than midazolam.[7,30,45] The reason for this apparent discrepency is the long elimination half-life is related to the slow elimination from highly lipophilic tissue compartments (e.g. fat) which is largely irrelevant in clinical situations.[21] Hughes *et al* discuss the pharmacokinetic profile of propofol that permits such a rapid recovery.[22] Propofol is extensively re-distributed into muscle, fat and other poorly perfused tissues. These tissues have a large capacity, but the rate of their equilibration with the central compartment is very slow. When an infusion of propofol is terminated, the concentration in the central compartment is much higher than that in these peripheral compartments, and redistribution continues to occur. The concentration in the central compartment continues to decline from both re-distribution and metabolism. Redistribution from the central compartment even after prolonged drug administration still occurs due to the fact that the capacity of the peripheral compartment is so large. The net result is a rapid decline in propofol concentration to levels below those required for hypnosis, permitting rapid awakening. As the concentration in the central compartment becomes lower than the peripheral compartment, the drug will begin to move back into the central compartrment. The rate of this transfer is slow which results in a long elimination half-life, allowing the concentration of propofol in the central compartment to remain at subtherapeutic levels. Thus the complete elimination of propofol may take hours or even days without any appreciable effect on clinical recovery.

Propofol has a more rapid blood-brain equilibrium (1-2 min.)[30] compared to midazolam (2-4 min)[31,32] which means that the levels of sedation can be more rapidly increased in anticipation of an imminent noxious stimuli.[19]

Pharmacodynamics

Pharmacodynamics describes the responsiveness of receptors to drugs and the mechanism by which these effects occur. During induction of anesthesia, propofol has been associated with decreased systolic blood pressure of 10-20 mm Hg and in diastolic pressure of 5-15 mm Hg.[7,34] Apnea during induction is also common, with some investigators reporting 25-30% incidence of apnea.[35,36] However, the doses used for sedation are much smaller, and these side effects were not significant when propofol was used for sedation during lower limb surgery under spinal anesthesia.[36] Rosa *et al* concluded that sedative doses of propofol had no adverse effects on tidal volume, minute ventillation, end tidal carbon dioxide tension, or arterial blood gas values.[37]

In healthy patients, midazolam 0.15mg/kg IV over 15 seconds, produced significant reductions in systolic (5%) and diastolic (10%) blood pressure and increased heart rate (18%).[38] Apnea occured in 20% of 1130 patients given varying doses of midazolam for induction of general anesthesia.[40] Cardiovascular depression is usually absent, but the most significant problem with midazolam is respiratory depression when given for conscious sedation.[8,20]

Amnesia and anxiety reduction are desirable outcomes after intravenous sedation. Forster reported that when 5 mg of midazolam was given as an intravenous pre-medication, hypnotic and anxiolytic effects appeared within 1-2 minutes and a memory picture shown at 4 min. after injection was not recalled by 78% of the patients.[40] These effects lasted for 30 minutes. A few studies have investigated the anxiolytic properties of

propofol. Ure *et al* concluded that patient controlled anxiolysis with subhypnotic doses of propofol was an effective premedication for patients presenting for day case surgery as compared to placebo.[46] Zachary *et al* reported on propofol's hypnotic and mood altering properties.[41] Propofol has also been found to be a euphoric agent causing positive mood changes.[53] Several investigators have reported on a greater degree of amnesia with midazolam sedation compared to sedation with propofol.[7,42,43]

The ideal anesthetic technique for ambulatory surgery should provide rapid recovery of cognitive and psychomotor functions. Smith *et al* divided the recovery process into three distinct phases.[17] The first phase, early recovery, usually described as emergence, describes the time at which the patient awakens from anesthesia and obeys simple commands. Intermediate recovery describes the return of cognitive and psychomotor function which permits discharge. Complete return to the pre-operative state with resumption of normal activities is described by late recovery.

Propofol's popularity as an intravenous anesthetic is due to its predictable recovery and favorable side effect profile.[17] Recovery is rapid after a single bolus or after repeated doses or a titrated continuous infusion, making propofol an effective anesthetic for short ambulatory surgical procedures.[30] Several authors reported more rapid recovery from propofol sedation compared to sedation with midazolam.[7,30,44] Shafer used the integrated pharmacokinetic-pharmacodynamic model to demonstrate that recovery from propofol will be faster than recovery from midazolam if a steady state concentration is maintained.[21] Recovery after continuous infusion of propofol for procedures lasting longer than 90 minutes was quicker than after continuous infusion with midazolam reversed with a single dose of flumazenil.[44] Quicker recovery was also seen after propofol sedation (22min) compared to midazolam sedation (49 min) during third molar surgery.[7]

Propofol has a very favorable side effect profile. Compared to methohexital, propofol causes significantly less nausea and vomiting.[53] Propofol has even been shown to be effective in treating nausea and vomiting when administered in subhypnotic doses.[48]

Propofol's euphoric properties have already been mentioned. Benzodiazepines have been known to cause disinhibitory reactions characterized by increased talkativeness, anxiety and excitement.[50] It appears that these reactions occur more commonly in younger patients.[50]

Propofol also provides some non- hypnotic therapuetic applications. Propofol has been discovered to have anti-pruritic effects.[51] The administration of subhypnotic doses of propofol to relieve neuraxial opiod-induced pruruitis was found to be effective in approximately 80% of patients.[52]

Propofol appears to have analgesic properties. Miranda investigated two identical groups of women who underwent caeserian section and received either propofol or methohexital.[53] In the immediate post-operative period the propofol group required significantly less analgesia.

METHODS

Sixty ASA class I or II adults, age 16-40, in need of removal of at least two third molars, were included into the study after signing informed consent. Patients were excluded from the study if they reported a history of psychiatric illness, chronic use of CNS depressants or antidepressants, alcohol abuse, were morbidly obese, had an active infection with systemic symptoms, were pregnant or reported a history of anesthetic related complications. Patients were treated at the University of North Carolina Department of Oral and Maxillofacial Surgery or at a private office in Durham North Carolina.

At the consultation appointment a complete medical history was elicited from the patient and oral and radiographic examinations were completed to confirm the need for the extractions. Pre-operatively patients completed the Corah anxiety scale (figure 1) and were instructed to line walk six feet. Patients were randomly assigned to receive either propofol and fentanyl or midazolam and fentanyl based on the last digit of their social security number. Patients were instructed to fast 8 hours prior to their surgical appointment and to bring a responsible person to accompany them home following sedation.

On arrival for surgery, baseline physiologic parameters were measured prior to receiving any medications. A 20 gauge intravenous catheter was placed, usually in the antecubital fossae whenever possible, or utilizing the largest available vein. Intravenous fluids were either 0.9% normal saline or 5% dextrose water. Oxygen at 4L/min was delivered via nasal cannula. Patients were shown a drawing of a common object prior to receiving any medications. Dexamethasone, 8 mg, (American Regent Laboratories, Inc., Shirley, NY) , was the first drug administered followed by 100 mcg of fentanyl (Elkins-

Sinn Inc., Cherry Hill, NJ) delivered over 2 minutes. Subjects then randomly received either propofol (Stuart, Wilmington, DE) or midazolam (Roche Laboratories, Nutley, NJ) titrated to the same endpoint of slurred speech, lid ptosis and patient report of relaxation without loss of consciousness. Propofol was administered via a Bard infusion pump (Baxter Healthcare, Deerfield Il) starting with 300 mcg/kg boluses IV to the endpoint. Sedation was maintained with a continuous infusion. Two to five mg of midazolam was given slowly to the endpoint. Twenty-five percent of the initial bolus was given to maintain sedation. A maximum of 14.4cc of Lidocaine 2% with 1:100,000 epinephrine was used to achieve local anesthesia. Marcaine, 0.5% with 1:200,000 epinephrine, 1.8cc, was used for each inferior alveolar nerve block. Efficacy of the local anesthesia was assessed by probing the buccal and lingual surfaces of the third molar with a Woodson elevator. Physiologic parameters including blood pressure, pulse, respiratory rate, expired CO2, and oxygen saturation measured via pulse oximetry were recorded every 5 minutes until the end of the procedure. Adverse side effects including pain on injection of sedative agents, cardiac arrythmias and apneas greater than 20 seconds were recorded.

The surgical procedure was started 5 minutes after the completion of the local anesthesia. If the patient did not tolerate the procedure due to inadequate local anesthesia or inadequate sedation, the case was recorded as a drug failure. The surgical procedure was completed by the oral surgeon; the bur technique was used exclusively. At 5 and 15 minutes intra-operative periods, patients were assigned a alertness score (figure 2) and an cooperation score (figure 3) by an observer. Patients were asked about the level of pain experienced on a scale of none to severe, and were shown a picture of a common object at the 5 and 15 minutes intra-operative periods. At completion of the surgical procedure the propofol infusion was discontinued. The surgeon assigned trauma scores for each tooth removed on a scale of mild to severe. The surgeon also rated the sedation on a scale of poor to excellent.

Following completion of the surgery the patient was immediately transferred to a separate recovery room. Subjects completed the Treiger dot test immediately and at 10, 20 and 45 post-operative minutes. Subjects completed ambulatory function tests at 10, 20 and 45 post-operative minutes to measure recovery (figure 4). Physiologic variables were recorded at 15 minute intervals until the time of discharge up to 45 minutes. Retrograde and anterograde amnesia were assessed by recording patients recall of specific events and pictures shown before and after induction of anesthesia (figure 5). Prior to discharge, patients rated their sedation on a scale of poor to excellent. Patients returned within one post-operative week for routine follow-up and were again queried to assess amnesia.

The patients and surgery characteristics (age, weight, surgery time) and anesthetic characteristics (induction and infusion dose of propofol and midazolam, and local anesthesia) were described by means, standard deviation and ranges. Level of significance was set at 0.01 for all comparative analyses. An unpaired t test was used to test for significant difference between the two groups of study patients. The Corah anxiety score, trauma score, number of teeth extracted, cooperation scores, alertness scores, pain scores, sedation scores, psychomotor recovery, Treiger dot tests and percent recall differences were tested using the Cochran Mantel Haenszel Row Mean Score Test. Physiologic variables (blood pressure, respiratory rate, carbon dioxide level, oxygen saturation and heart rate) were analyzed by repeated measures analysis of variance with comparisons between each post-surgical time and baseline. Unpaired t tests were used to compare study groups at each time interval. Comparison between groups for physiologic variables was not performed beyond the 20 minute time period because very few patients required observation beyond that time.

RESULTS

Of the sixty volunteers who met the inclusion and exclusion criteria, 2 subjects in the propofol group and 1 subject in the midazolam group were excluded because of the inability to adequately tolerate the surgical procedure wtih intravenous sedation and required deepening to a general anesthetic. The mean age, weight, ASA class, sex and race distribution of the remaining 57 patients are listed in table 1. There were no statistically significant differences between the groups. There were no statistically significant differences in the pre-operative baseline vital signs which included blood pressure (BP), heart rate (HR), respiration rate (RR), expired carbon dioxide (CO2), and oxygen saturation (Sa02) between the two groups.

Patients in the M + F group received a mean induction dose of 4.7 mg of midazolam with a mean bolus of 0.60 mg to complete an average 21.0 minute surgery. Patients in the P + F group received a mean induction dose of 839.6 mcg/kg with an mean infusion rate of 118.8 mcg/kg/min to complete an average 20.7 minute surgery (Table 2). The amount of local anesthetic administered was similar between groups (Table 2). There were no statistically significant differences in the Corah anxiety scores between groups. The number of teeth extracted or the surgical trauma scores was not different between groups (Table 1). Pain on injection of propofol was reported by 25% of the patients.

There were no statistically significant differences in the overall mean values of SBP, DBP, RR and SaO2 ($p > 0.5$) between the two groups. Both groups demonstrated a significant increase in heart rate at the 10 ($p \leq 0.005$) and 15 minute ($p \leq 0.0001$) periods (Graph 1). No cardiac arrythmias were recorded for either drug treatment group. No significant respiratory depression were recorded; there were no significant decreases in

respiratory rate (Graph 2) or increases in expired CO2 (Graph 3). The P + F group demonstrated larger increases in expired CO2 at the 5 and 15 minute periods, but the differences were not significant. Average oxygen saturation were measured by pulse oximetry and remained above 99% during the entire procedure in both groups (Graph 4). Two subjects in the M + F group and one subject in the P + F group had apneas > 20 seconds in duration. Patients who became apneic began breathing when stimulated and none required assisted ventillation. Both groups exhibited decreases in DBP from baseline at the 5, 15 and 20 minute periods and the differences were statistically significant ($p = 0.0001$) (Graph 5). Both groups also exhibited a drop in systolic blood pressure at the 5 minute period ($p = 0.0003$) and the differences were statistically significant (Graph 6).

The P + F group was less cooperative than the M + F group at both 5 ($p = 0.019$) and 15 ($p = 0.002$) intra-operative minutes and the differences were statistically significant (Graph 7). There were no statistically significant group difference in alertnesss scores (Graph 8), report of intra-operative pain (Graph 9), patient, observer, or surgeon's evaluation of sedation (Graph 10).

Post-operative psychomotor recovery scores (Graph 11) and Treiger dot test scores (Graph 12) between groups were not statistically significant. Amnesia of pictures shown during the procedure and actual clinical events was greater for the M + F group (37.7% recall) compared to the P + F group (45.0% recall), but the differences were not statistically significant (Graph 13).

DISCUSSION

The results of this study agree with other studies and suggest that propofol is a safe and efficacious drug for sedation during outpatient oral surgical procedures. The mean induction dose of the M + F group (4.7 mg and a mean bolus of .60 mg.) was equivalent to the mean total dose of 5.7 mg of midazolam administered with fentanyl in the multicenter study by Dionne *et al* during the removal of impacted third molars in 185 patients with a mean surgical time of 24.4 minutes.[54] The mean induction dose of the P + F group (839.6 ucg/kg with a mean infusion rate of 118.8 ucg/kg/min) was slightly higher than the mean infusion rate of 83 ucg/kg/min reported by Rodrigo and Jonsson for IV sedation during the removal of third molars.[7] Difference between our study and Rodrigo and Jonsson may be that during sedation verbal contact was maintained with patients in the Rodrigo and Jonsson study where patients in our study were at a deeper levels of sedation. In the present study the mean alertness score was 3.27 which was the numerical value at which the patient responded only after the patients name was called loudly and repeatedly (Figure 1). Taken together the doses of midazolam and propofol used in our study are similar to the mean doses required to provide conscious sedation in other studies.

The most common adverse side effect reported by this study was pain on injection of propofol in 25% of the subjects. In contrast, none of the midazolam group had pain on injection. The incidence of pain during injection of propofol during sedation has been reported to be in the range of 33-50%.[17] The exact mechanism responsible for the pain induced during propofol injection are not known, however, one cause may be the activation of the kinin cascade system.[55] Klement and Arndt discovered that pain was caused by the drug itself rather than the formulation.[56] When 2% xylocaine mixed with propofol before infusion, the incidence of pain on injection was reduced to 6%.[57] In our

study there was a 6 % incidence of apnea in the M + F group. Bailey *et al* reported an incidence of apnea (no spontaneous respiratory effort for 15 seconds) in 6 of 12 patients (50%) receiving fentanyl (2 ucg/kg) and midazolam (0.05 mg/kg).[58] Their study did not include surgical stimulation and the drugs were both given within a 1 minute duration. In our study fentanyl was administered over two minutes followed by slow titration of midazolam. Dionne et al reported that 48-50% of subjects receiving 100 mcg fentanyl and midazolam during the removal of impacted third molars demonstrated apnea (> 30 sec).[54] In the present study there was an 4% incidence of apnea in the P + F group. When propofol and alfentanyl were used for sedation for transvaginal oocyte removal there was no clinical evidence of respiratory depression.[61] Candaleria and Smith administered 10 mcg/kg of alfentanyl and propofol (infusion rate of 150 - 200 mcg/kg/min) during outpatient general anesthesia with no evidence of respiratory depression.[62] However, Shafer stated that propofol was a potent respiratory depressant and should be administered for sedation only by anesthesiologists or other personnel trained in airway management.[19] Stokes and Hutton demonstrated a lower incidence of apnea in patients who received slow induction doses of propofol compared to patients who received a rapid induction dose.[63] The review of the literature suggests that other factors can affect the incidence of apnea when propofol is used for outpatient anesthesia. Further studies will be required to differentiate the effect of rate of infusion and apnea in a clinical study.

Cardiovascular parameters remained stable throughout induction, maintainance and recovery in both groups. Systolic and diastolic blood pressures were lower in both groups at the 5 minute intra-operative period and the differences were statistically significant. In other studies, induction of general anesthesia with midazolam and propofol produced a reduction in systolic and diastolic blood pressures.[34,38] Doses of propofol and midazolam adjusted for sedation do not generally produce cardiovascular depression.[8,20,36] Fentanyl, known for its hypotensive effects because of its potential to decrease systemic vascular resistance,[64] probably contributed to effect of the test drugs

used for sedation in this study. The differences in HR, SBP, DBP were not clinically important and and no interevention were required.

The mean cooperation scores in the P + F group was significantly less than the M + F group at both 5 and 15 intra-operative minutes. The investigators clinical impression was that some subjects receiving P + F were more talkative and disoriented than most subjects receiving M + F. These findings are similar to those of Rodrigo and Johnson who reported that 51% of patients receiving propofol for sedation exhibited increased talkativeness that sometimes interfered with the operative procedure.[7]

Both the Treiger dot test scores and psychomotor recovery scores were similar between groups. In contrast, several other studies demonstrated different recovery patterns in patients receiving propofol or midazolam.[7,30,44] Steib *et al* investigated recovery after total intravenous anesthesia with either propofol or midazolam reversed or not with flumazenil.[44] Thirty patients scheduled for outpatient surgery were randomly allocated to receive either propofol (n = 10) or midazolam (n = 20) continuous infusion with alfentanyl. Flumazenil was administered until subjects opened their eyes on command or received a maximum dose of 1 mg. Recovery scores from deletion of a's, Newman test and postbox tests were significantly better for the propofol group at 45, 90 and 180 minutes after the end of anesthesia. In half of the midazolam patients flumazenil did not improve scores when compared to those receiving midazolam alone. In contrast , Ochs *et al,* discovered that recovery time was significantly decreased in 93% of patients who received a maximum of 1 mg of flumazenil after sedation with intravenous midazolam.[62] Rodrigo and Jonsson measured the deletion of P's and a modified Rhomberg test in patients who received continuous infusion of propofol (recovery = 22 min) and midazolam (recovery = 49 min) and demonstrated quicker recovery times for propofol.[7] Since it is important to ensure that all patients are maintained at a similar depth of anesthesia to compare recovery, the difference between studies may be due, in part, to differences in

anesthetic depth.[17] It may be difficult to be certain that all patients were at comparable depths of anesthesia which may account for differences between studies.

In our study, antegrade amnesia was greater for the M + F group compared to the P + F group, but the differences were not statistically significant. Rodrigo and Jonsson demonstrated similar results in patients who received midazolam (30 %) versus patients who received propofol (24 %).[7] The differences were not statistically significant. Fanard *et al* found no significant difference in the incidence of amnesia (60% after propofol and 56% after midazolam) in patients undergoing abdominal or orthopaedic surgery under epidural anesthesia and intravenous sedation.[63]

Sedation scores rated by surgeon, observer and the patients corresponded to rating between good and excellent, thus patients reported high satisfaction for both drug treatment groups. Rodrigo and Jonsson found that patients reported a significant preferrence for midazolam sedation compared to propofol ($p< 0.01$)[7]

CONCLUSIONS

Propofol appears to be an safe and efficacious alternative to midazolam for use as an intravenous sedative agent during the removal of third molars on an outpatient basis. Cardiovascular and respiratory variables were similar between groups. Both groups experienced a small percentage of apneic episodes during sedation, but no patients required ventilation. There was no difference between groups in recovery parameters. Both groups had similar depths of sedation, but the patients in the propofol group were less cooperative to a statistically significant degree. Pain on injection of propofol was a notable adverse side effect. Antegrade amnesia was greater for the midazolam group but the difference was not statistically significant. Patient and surgeon satisfaction was high for both groups. Our study shows that propofol was an acceptable alternative for outpatient oral surgical procedures.

Table 1

PATIENT AND SURGERY CHARACTERISTICS

	P + F (n = 24)		M + F (n= 33)	
	Mean (+/- SD)	Range	Mean (+/- SD)	Range
Age (yrs)$	25.5 (5.7)	19 - 41	23.1 (3.9)	17 - 32
Sex (male)	9		15	
Sex (female)	15		18	
Race	Cau = 17		Cau = 15	
Weight (lbs)*	151.1 (28.6)	115 - 210	155.1 (30.6)	88 - 215
Surgery Time &	20.6 (9.2)	8 - 40	21.0 (11.1)	8 - 45
Corah Anxiety Score^	9.5 (3.2)	4 - 16	8.9 (3.3)	5 - 19
Trauma Score**	1.37 (.40)	.75 - 2.0	1.51 (.50)	.75 - 3.0
Number of Teeth Ext.#	3.67 (0.56)	2 - 4	3.58 (0.71)	2 - 4

Unpaired t Test:
$ p = 0.0558
* p = 0.6205
& p = 0.9023

Mantel Haenszel Row Mean Score Test:
^ p = 0.507
** p = 0.253
# p = 0.601

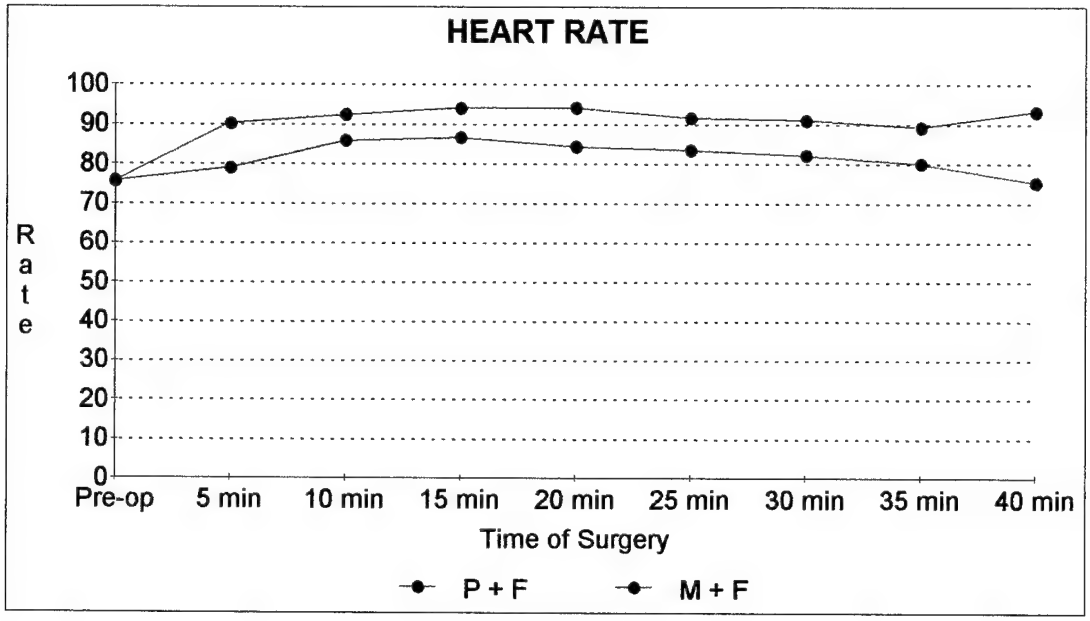
Table 2

ANESTHETIC CHARACTERISTICS

	P + F (n = 24)		M + F (n= 33)	
	Mean (+/- SD)	Range	Mean (+/- SD)	Range
Propofol Ind. (mcg/kg)	839.58(243.2)	500-1500		
Propofol Inf. (mcg/kg/min)	118.8(33.7)	50-175		
Midazolam Ind. (mg)			4.72(1.82)	2.0-8.0
Midazolam Bolus			.59(1.10)	0.0-4.0
2% Xylo/1:100k epi (cc)&	7.79(1.96)	3.60-14.40	7.52(2.09)	3.60-12.60
.5%mar/1:100k epi (cc) *	2.84(1.49)	0.0-5.40	3.16(1.01)	0.0-3.60

Unpaired t test:
& p = 0.62
* p = 0.38

Graph 1



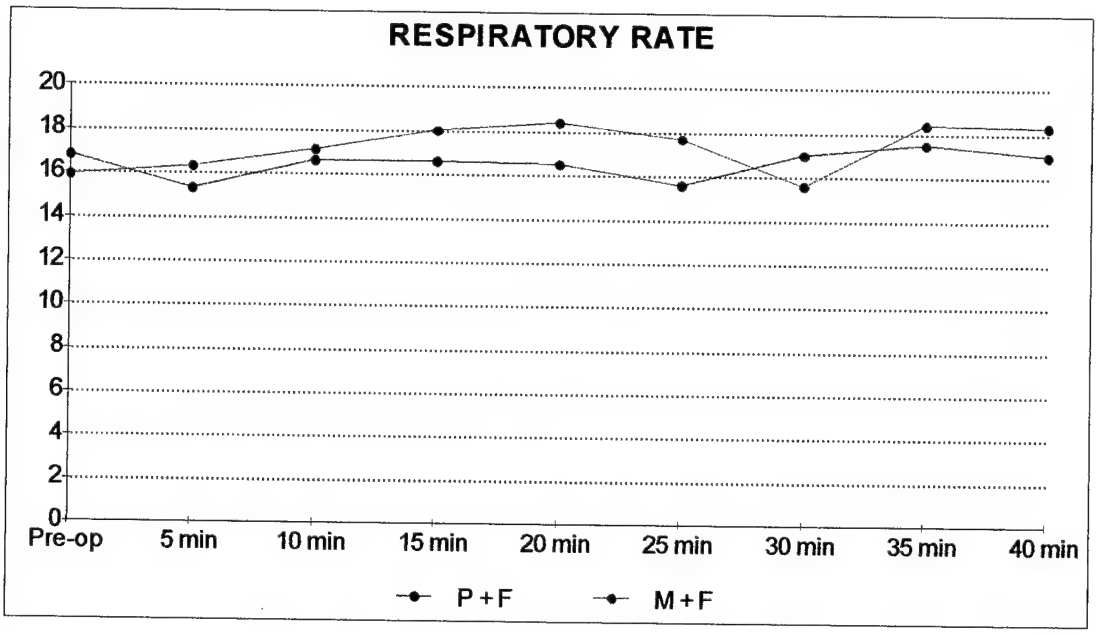
Unpaired t Test:

Difference between groups at 5 min $p = 0.0005$
20 min $p = 0.04$

Repeated Measures Analysis of Variance:

P + F: Difference between pre-op and 10 min $p = 0.005$
pre-op and 15 min $p = 0.0005$
M + F: Difference between pre-op and 5, 10, 15 min $p = 0.0001$

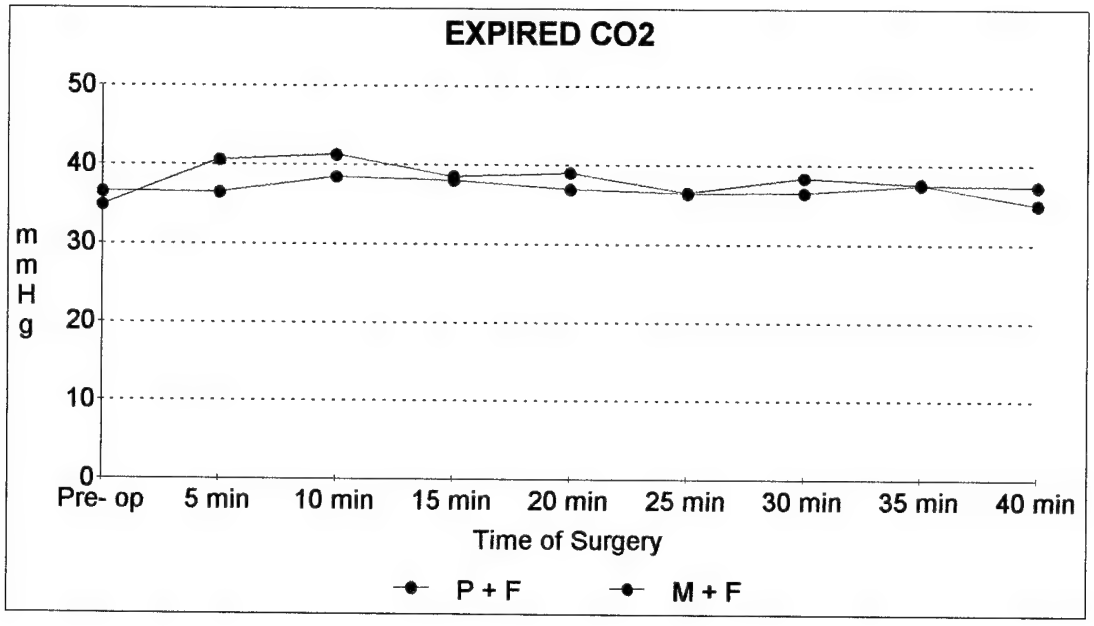
Graph 2



Repeated Measures Analysis of Variance:

Change over time in respiration rate $p = 0.17$

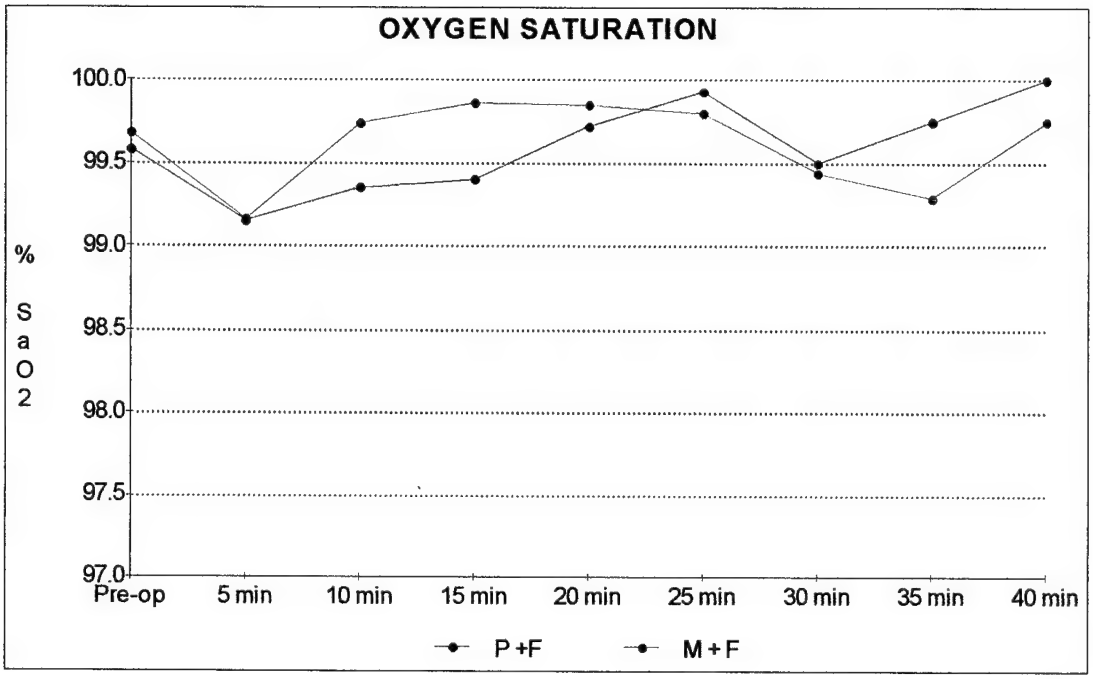
Graph 3



Repeated Measures Analysis of Variance:

Pattern of Change over time in expired CO2 between groups $p = 0.02$

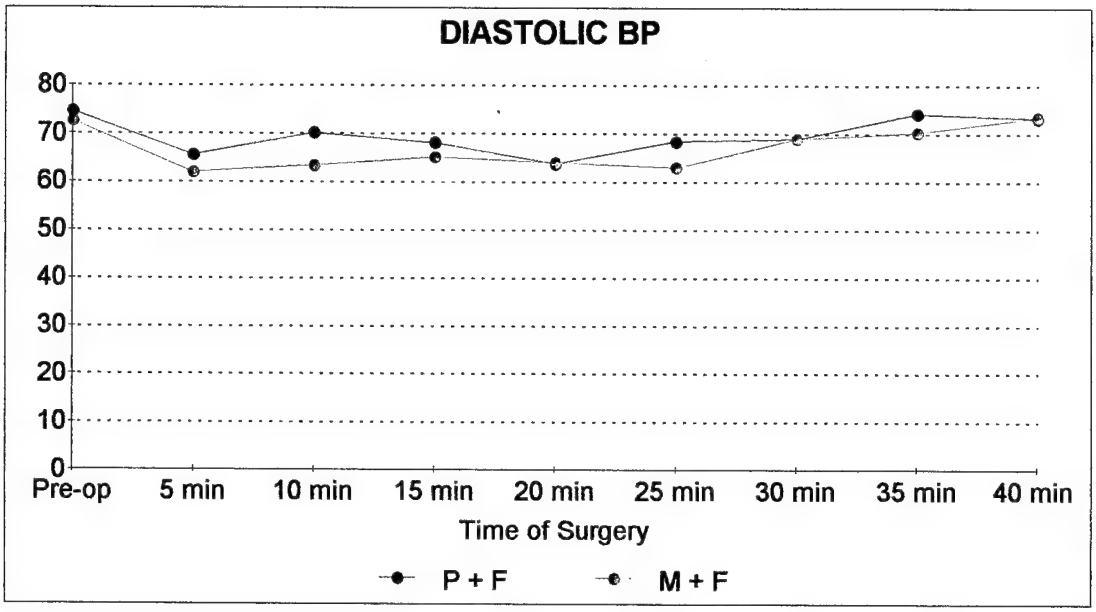
Graph 4



Repeated Measures Analysis of Variance:

Change over time in oxygen saturation $p = 0.12$

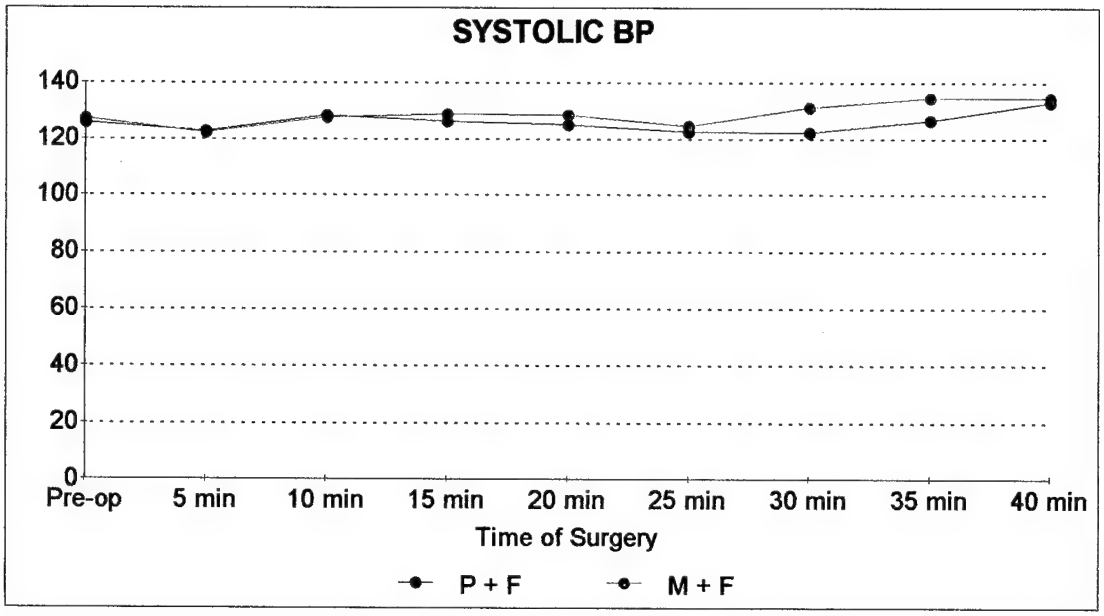
Graph 5



Repeated Measures Analysis of Variance:

Change over time in diastolic BP between pre-op and each mean for 5 min, 15 min and 20 min, $p = 0.0001$

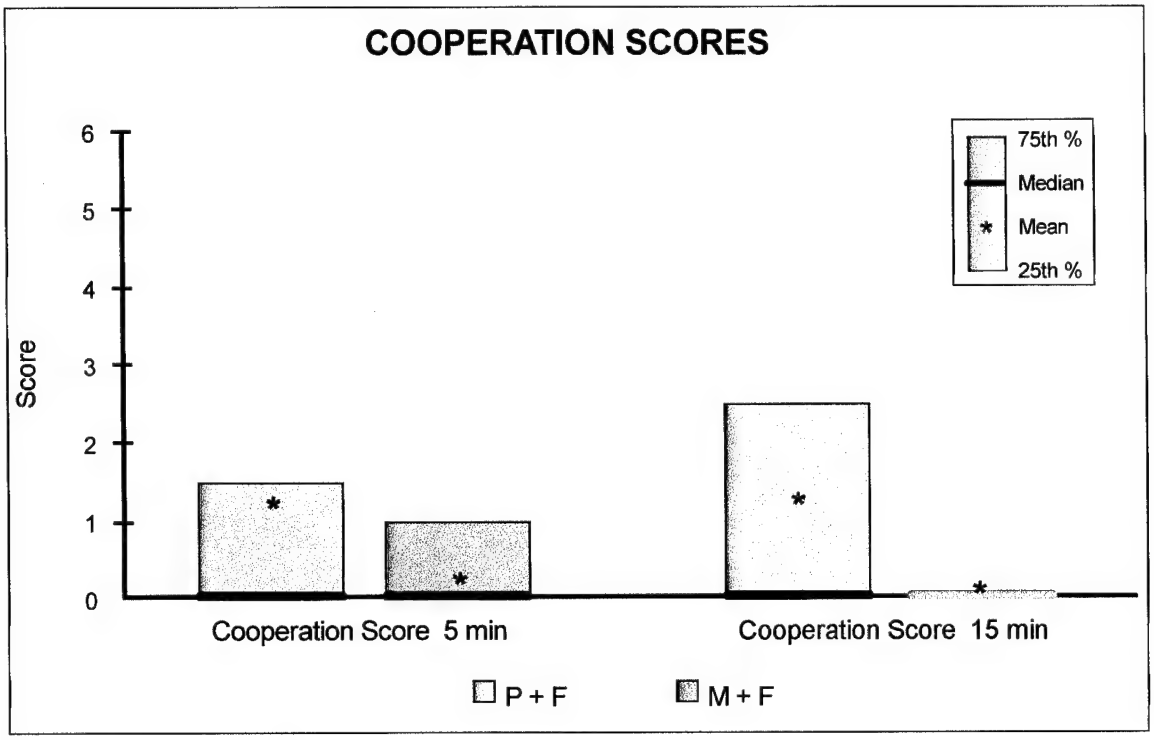
Graph 6



Repeated Measures Analysis of Variance:

Change over time in systolic BP between pre-op and 5 min, $p = 0.0003$

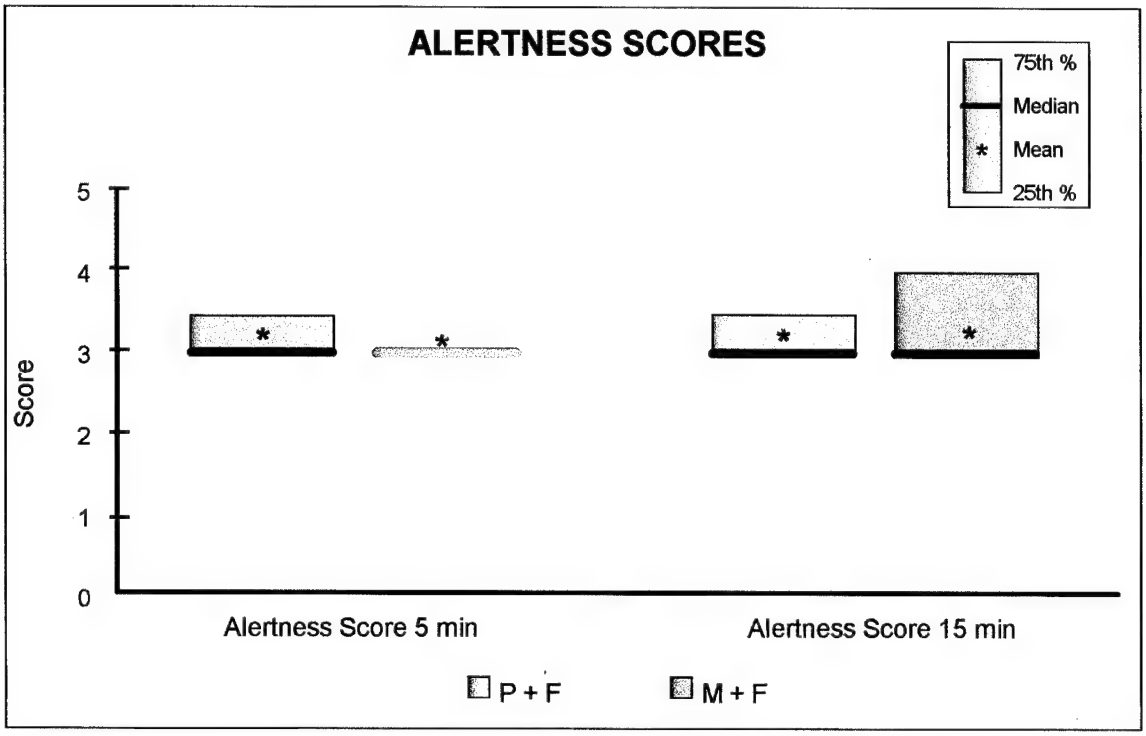
Graph 7



Cochran Mantel Haenszel Row Mean Score Test:

Cooperation Score 5 min $p = 0.019$
Cooperation Score 15 min $p = 0.002$

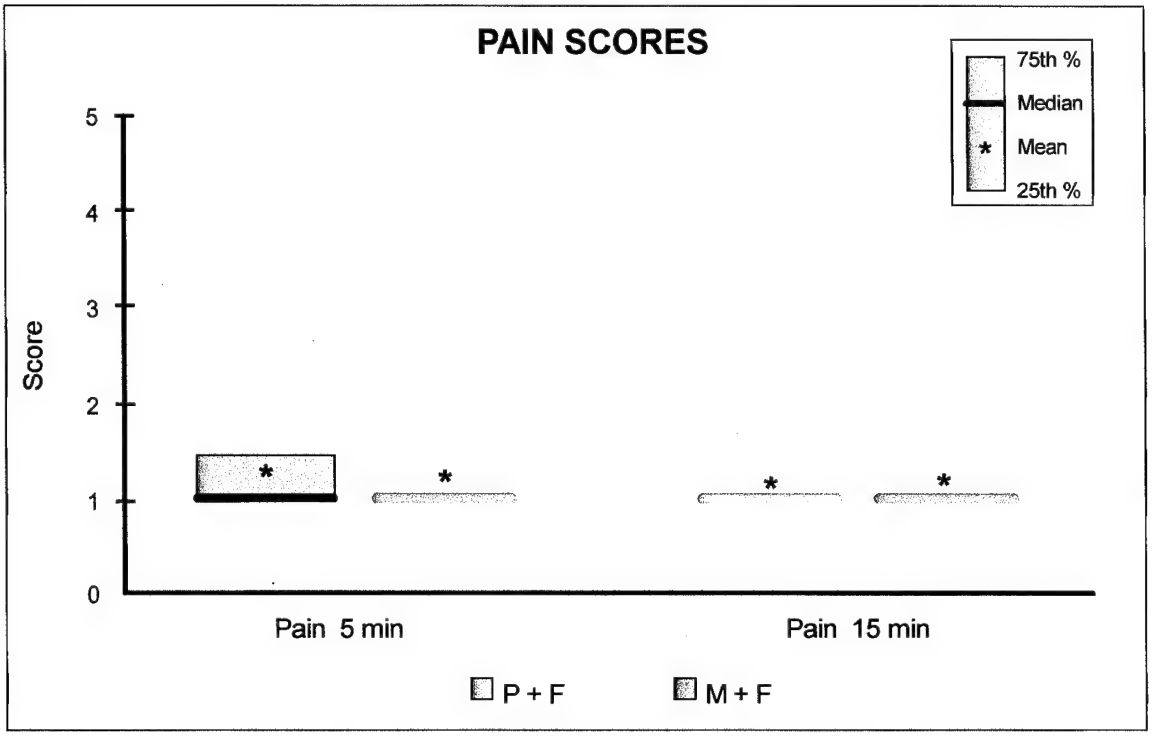
Graph 8



Cochran Mantel Haenszel Row Mean Score Test:

5 min Alertness Score $p = 0.548$
15 min Alertness Score $p = 0.909$

Graph 9



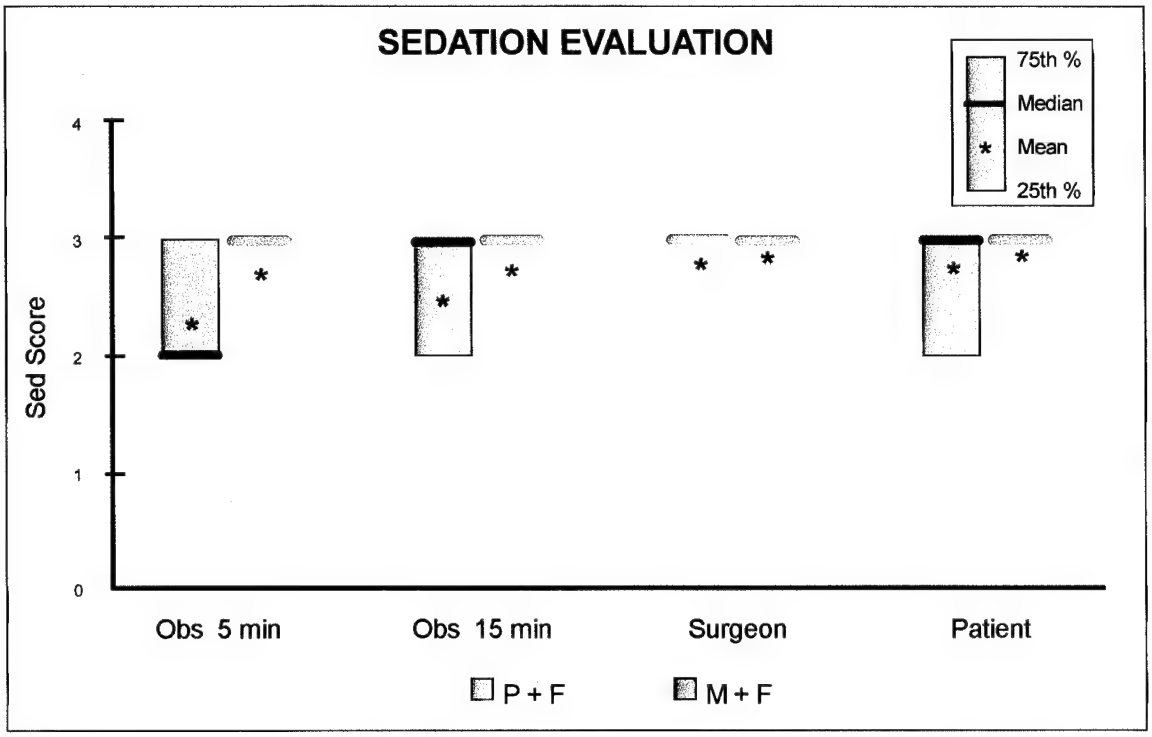
Pain Scores:

None = 0
Mild = 1
Moderate = 2
Severe = 3

Cochran Mantel Haenszel Row Mean Score Test:

Pain 5 min $p = 0.175$
Pain 15 min $p = 0.458$

Graph 10



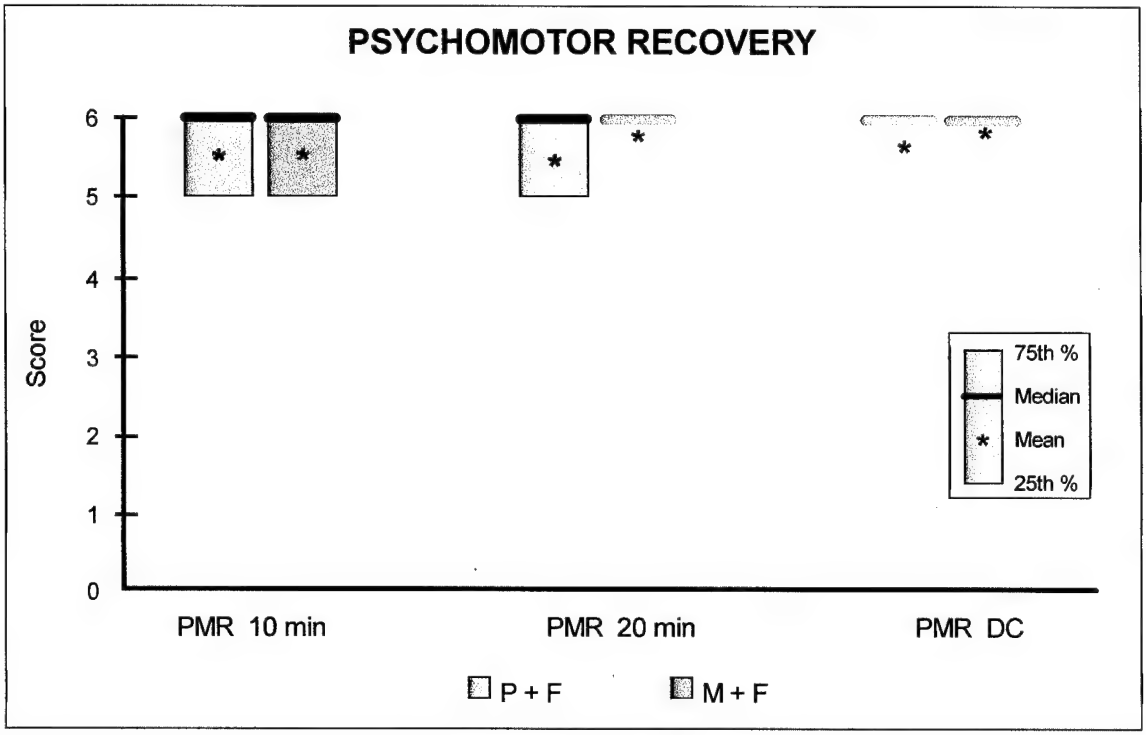
Sedation Rating:

Poor	= 0
Fair	= 1
Good	= 2
Excellent	= 3

Cochran Mantel Haenszel Row Mean Score Test:

Observer 5 min	p = 0.033
Observer 15 min	p = 0.115
Surgeon	p = 0.450
Patient	p = 0.240

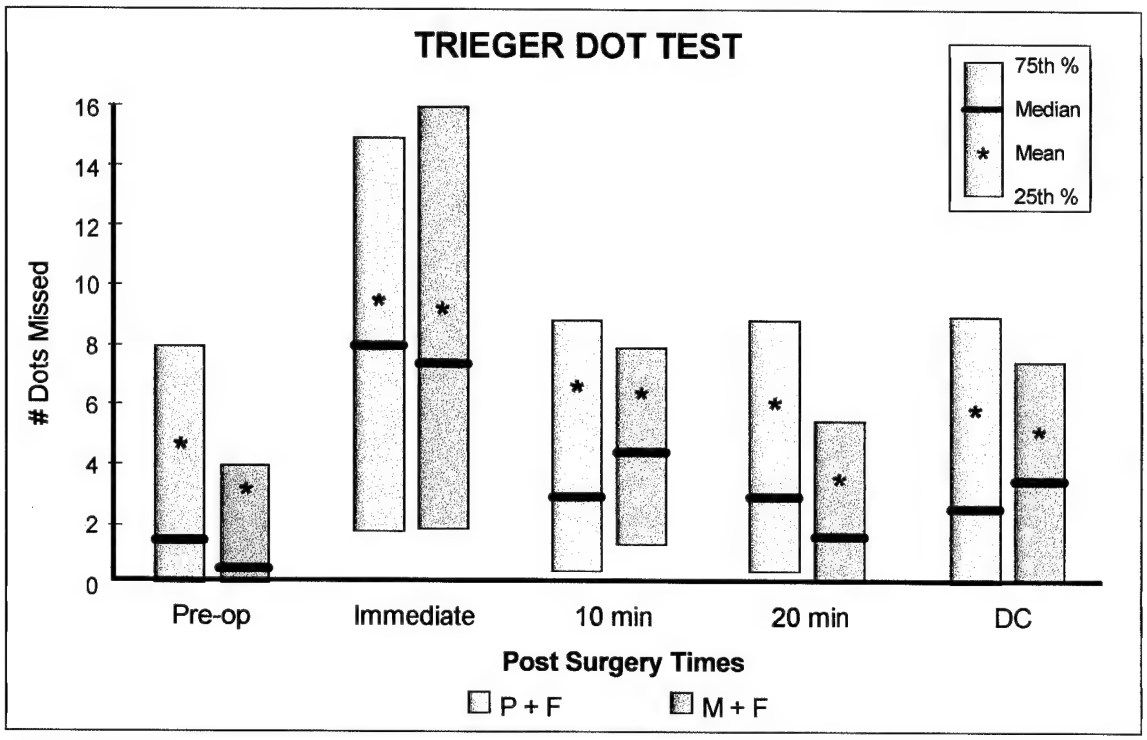
Graph 11



Cochran Mantel Haenszel Row Mean Score Test:

Psychomotor Recovery Score 10 min	p = 1.000
Psychomotor Recovery Score 20 min	p = 0.061
Psychomotor Recovery Score Discharge	p = 0.189

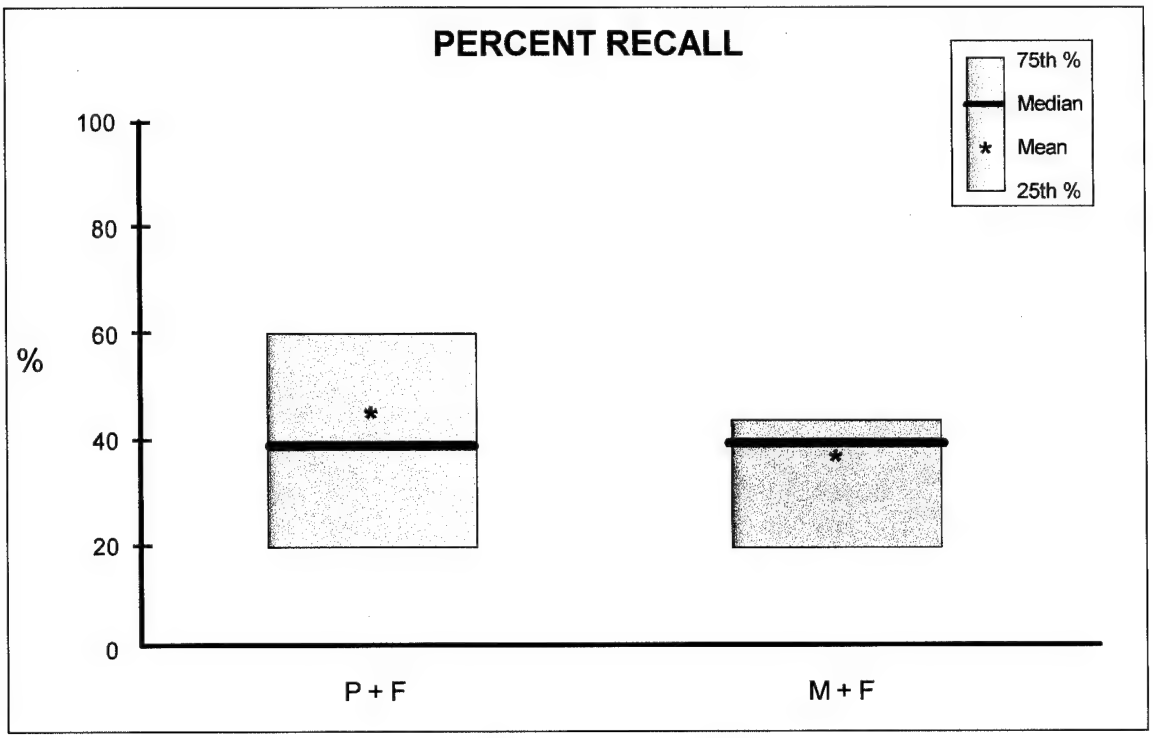
Graph 12



Cochran Mantel Haenszel Row Mean Score Test:

Immediate	p = 0.898
10 min	p = 0.836
20 min	p = 0.085
DC	p = 0.598

Graph 13



Cochran Mantel Haenszel Row Mean Score Test:

Percent Recall $p = 0.232$

Figure 1

SEDATION STUDY: CORAH ANXIETY SCALE

PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ___ ___ ___

DATE ___/___/___

INSTRUCTIONS: Check the response which best describes your feelings.

1. If you had to go to the dentist tomorrow, how would you feel about it?

____ I would look foreward to it as a reasonably enjoyable experience.
____ I wouldn't care one way or the other.
____ I would be a little bit uneasy about it.
____ I would be afraid that it would be unpleasant and painful.
____ I would be afraid of what the dentist might do.

2. When you are waiting in the dentist's office for your turn in the chair, how do you feel?

____ relaxed
____ a little uneasy
____ tense
____ anxious
____ So anxious that I sometimes break out in a sweat or almost feel physically sick.

3. When you are in the dentist's chair waiting while he gets his drill ready to begin working on your teeth, how do you feel?

___ relaxed
___ a little uneasy
___ tense
___ anxious
___ So anxious that I sometimes break out in a sweat or feel physically sick.

4. You are waiting in the dentist's chair to have your teeth cleaned. While you are waiting and the dentist is getting out his instruments which he will use to scrape your teeth around the gums, how do you feel?

___ relaxed
___ a little uneasy
___ tense
___ anxious
___ So anxious that I sometimes break out into a sweat or almost feel physically sick.

CORAH SCORE _____

Figure 2

SEDATION STUDY: ALERTNESS SCALE

PATIENT NUMBER____ ____ ____ PATIENT INTIALS ___ ___ ___
CLOCK TIME_____ RATER_____
OBSERVATION:_____BASELINE____ 5 min._____15 min.

INSTRUCTIONS: Rate the patient's level of alertness within each of the three categories. Assign the composite score corresponding to the lowest level checkes in any of the categories.

RESPONSIVENESS	EXPRESSION	EYES	COMPOSITE SCORE
___ Responds readily to name spoken in normal tone	___ Normal	___ Clear, no ptosis	____(5) alert
___Responds lethargically to name spoken in normal tone	___ Mild relaxation	___Glazed or mild ptosis <1/2 eye	____(4)
___Responds only after name is called loudly and repeatedly	___Marked relaxation (slack jaw)	___Glazed& marked ptosis > 1/2 eye	____(3)
___Responds only after mild prodding or shaking			____(2)
___Does not respond			____(1) deep sleep

ALERTNESS SCORE_____5 MIN_____15 MIN

INSTRUCTIONS: Show the patient a randomly selected picture card; have the patient verbally identify the object in the picture, then record below.

_____picture card identified by patient_____5 MIN _____ 15 MIN

_____patient unable to identify picture due to level of sedation (5 MIN)_____ 15 MIN

Figure 3

SEDATION STUDY: COOPERATION SCORE

PATIENT NUMBER___ ___ ___ PATIENT INITIALS___ ___ ___
DATE:___/___/___ CLOCK TIME _____
RATER:_____ Observer _____ Oral Surgeon

Please rate the efficacy of the sedation: 5 MIN 15 MIN

____Poor (0)
____Fair (1) OBS _____ _____
____Good (2)
____Excellent (3)

Please rate the patient's cooperation during the oral surgery:

Did the patient's movements during the local anesthesia or the extractions interfere or delay treatment? 5 15min

____ ___ No interfering movements (0)
____ ___ Minor movements, positioning remained appropriate (1)
____ ___ Minor movements, patient had to be re-positioned (2)
____ ___ Movements grossly interfered with the procedure (3)

To what extent did the patient verbalize discomfort duting the procedure?

____ ___ Not at all (0)
____ ___ Some verbalization, but did not indicate pain or discomfort (1)
____ ___ Some verbilization indicating pain or discomfort (2)
____ ___ Complained frequently during the procedure (3)

Did the patient show non-verbal signs of discomfort during the procedure?

____ ___ Not at all (0)
____ ___ Slight discomfort, occasional grimaces (1)
____ ___ Moderate discomfort, feet/hands tensed, tears in eyes (2)
____ ___ Marked discomfort apparent during prosedure (3)

Sum the numbers next to each response and record as the score of (0-9)

COOPERATION SCORE_____5 MIN _____15 MIN(OBS)
AT END OF CASE BY SURG_____

Figure 4

SEDATION STUDY: PSYCHOMOTOR RECOVERY

PATIENT NUMBER___ ___ ___ PATIENT INITIALS___ ___ ___
CLOCK TIME_____ RATER_____
DATE:____/____/____
OBSERVATION:_____Baseline_____Day of _____10 min. _____20 min.

INSTRUCTIONS: Evaluate each level of ambulatory function until the patient cannot perform the task normally. Do not attempt a task if the patient could not perform the previous easier task.

Ambulatory Function	Normal	Abnormal	Not attempted due to excessive sedation
1. Sits for 10 seconds	_____	_____	_____
2. Stands with support for 10 seconds	_____	_____	_____
3. Stands without support for 10 seconds	_____	_____	_____
4. Walks with support for six feet	_____	_____	_____
5. Walks without support for six feet	_____	_____	_____
6. Line-walks for six feet	_____	_____	_____

Mark the highest level of ambulatory function which the patient performed as the score below:

PSYCHOMOTOR RECOVERY SCORE:_____

Figure 5

SEDATION STUDY: POST -OPERATIVE DATA

15 MIN: BP___/___ HR___ RR___
PICTURES RECALLED: ____ PRE-OP _____ 5 min. _____15 min.
EVENTS RECALLED:_____ IV PLACED _____ LA INJECTIONS
_____ EXTRACTIONS _____ WALKING TO RECOVERY ROOM

30 MIN: BP___/___ HR____RR ____
PICTURES RECALLED:_____ PRE-OP ____ 5 min. ____15 min
EVENTS RECALLED: _____IV PLACED _____ LA INJECTIONS
_____EXTRACTIONS_____WALKING TO RECOVERY ROOM

45 MIN: BP___/___ HR____ RR_____
PICTURES RECALLED:____ PRE-OP_____ 5 min.____ 15 min.
EVENTS RECALLED:_____ IV PLACED_____LA INJECTIONS
_____EXTRACTIONS_____WALKING TO RECOVERY ROOM

AT TIME OF DISCHARGE: PATIENTS RATING OF EFFICACY OF SEDATION
POOR____ FAIR____ GOOD____ EXCELLENT____

1 WEEK POST-OP:
PICTURES RECALLED:_____ PRE-OP_____5 min. ____15 min.
EVENTS RECALLED:_____IV PLACED_____LA INJECTIONS
_____EXTRACTIONS_____WALKING TO RECOVERY ROOM

PROTOCOL VIOLATIONS, MISSING DATA

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